# In the United States Court of Federal Claims

**OFFICE OF SPECIAL MASTERS**

Filed: March 18, 2019

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| KENNETH BARON AND JAYME BARON, *on behalf of S.B., a minor*, | * | No. 14-341V<br>Special Master Sanders |
| Petitioners, | * | |
| v. | * | |
| SECRETARY OF HEALTH AND HUMAN SERVICES, | * | Hepatitis A ("HAV") Vaccine; Influenza ("Flu") Vaccine; *Althen*; anti-NMDAR Encephalitis |
| Respondent. | * | |

Ronald Craig Homer, Conway, Homer, P.C., Boston, MA, for Petitioners.
Claudia Barnes Gangi, United States Department of Justice, Washington, DC, for Respondent.

## DECISION[1]

On April 23, 2014, Kenneth and Jayme Baron ("Petitioners") filed a petition on behalf of S.B., pursuant to the National Vaccine Injury Compensation Program.[2] Petitioners allege that the Hepatitis A ("HAV") and influenza ("flu") vaccines S.B. received on November 11, 2011, caused her to develop anti-N-methyl D-aspartate receptor ("anti-NMDAR") encephalitis.

After carefully analyzing and weighing all the evidence and testimony presented in this case in accordance with the applicable legal standards, the undersigned finds that Petitioners have not met their legal burden. Petitioners have failed to provide preponderant evidence that the HAV and flu vaccinations S.B. received on November 11, 2011 caused her to develop anti-NMDAR encephalitis. Accordingly, Petitioners are not entitled to compensation.

[1] This decision shall be posted on the United States Court of Federal Claims' website, in accordance with the E-Government Act of 2002, 44 U.S.C. § 3501 note (2012) (Federal Management and Promotion of Electronic Government Services). **This means the Decision will be available to anyone with access to the Internet.** In accordance with Vaccine Rule 18(b), a party has 14 days to identify and move to delete medical or other information that satisfies the criteria in § 300aa-12(d)(4)(B). Further, consistent with the rule requirement, a motion for redaction must include a proposed redacted decision. If, upon review, the undersigned agrees that the identified material fits within the requirements of that provision, such material will be deleted from public access.

[2] The Program comprises Part 2 of the National Childhood Vaccine Injury Act of 1986, 42 U.S.C. §§ 300aa-10 et seq. (hereinafter "Vaccine Act," "the Act," or "the Program").

## I. Procedural History

Petitioners filed twenty-one medical records on May 15, 2014, and a compact disk containing two additional medical records on May 27, 2014. *See* Pet'rs' Exs. 1–21, ECF Nos. 9–11; *see* Notice of Intent to File Pet'rs' Exs. 22–23 on CD, ECF No. 12. On July 10, 2014, Petitioners filed a statement of completion. ECF No. 15.

Respondent filed his Rule 4(c) Report on September 22, 2014. ECF No. 20. In his report, Respondent agreed with the diagnosis of anti-NMDAR encephalitis and agreed that S.B. had suffered the residual effects or complications of this injury for more than six months. *Id.* at 8. However, Respondent argued that compensation is not appropriate because Petitioners had "not offered sufficient reliable evidence to establish a causal relationship between S.B.'s . . . vaccinations and her anti-NMDAR encephalitis." *Id.*

Petitioners then filed two additional medical records on November 4, 2014. Pet'rs' Exs. 24–25, ECF No. 22. On June 25, 2015, Petitioners filed an expert report from Dr. Murray Engel. Pet'rs' Exs. 26–27, ECF No. 34. Respondent filed his responsive expert report from Dr. Jessica A. Panzer on November 23, 2015. Resp't's Exs. A–B, ECF No. 39. Respondent filed an additional twelve pieces of medical literature on December 12, 2015. Resp't's Exs. C–N, ECF No. 41. Petitioners filed their first supplemental expert report on April 22, 2016, and their second supplemental expert report on August 10, 2016. Pet'rs' Exs. 28–29, ECF Nos. 44, 50. On May 15, 2017, Respondent filed an additional eight exhibits, including a new expert report and supporting medical literature from Dr. Eric Lancaster.[3] Resp't's Exs. BB–II, ECF No. 57.

An entitlement hearing occurred on August 28, 2018. *See* Hearing Order, ECF No. 63. Petitioners filed four additional medical records before the hearing. Pet'rs' Exs. 32–35, ECF Nos. 72–75.

## II. Factual Background

S.B. was born healthy on February 10, 2010, at Next Generation Pediatrics. Pet'rs' Ex. 6 at 2. On July 10, 2010, S.B. had her five-month well child visit, and doctors noted that she was a "healthy female infant [with] improving [gastroesophageal reflux disease[4]]." *Id.* at 8. S.B. had her ten-month well child visit on December 13, 2010, where she was diagnosed with right otitis media,[5] but was otherwise healthy and developing normally. *Id.* at 27. In addition, S.B. received her first flu vaccination at that visit. *Id.*; Pet'rs' Ex. 1 at 3. On December 15, 2010, S.B.'s

[3] For personal reasons, Dr. Panzer was unable to continue as an expert in this case. Therefore, Respondent notified the court on February 2, 2017, that he would need to provide in a new expert. ECF No. 54.

[4] Gastroesophageal reflux disease is "any condition noted clinically or histopathologically that results from gastroesophageal reflux, ranging in seriousness from mild to life threatening; principal characteristics are heartburn and regurgitation." *Dorland's Illustrated Medical Dictionary* 533 (32nd ed. 2012) [hereinafter "*Dorland's*"].

[5] Otitis media is "inflammation of the middle ear." *Dorland's* at 1351.

pediatrician prescribed her a ten-day course of Cefzil[6] to correct her right otitis media. Pet'rs' Ex. 6 at 27.

On December 16, 2010, S.B. suffered a seizure while on a flight from New York City to Fort Lauderdale, Florida. Pet'rs' Ex. 21 at 11. The seizure lasted for approximately thirty seconds, and S.B. was given a crushed 500 mg adult Tylenol tablet dissolved in juice. *Id.* Upon landing, S.B. had a temperature of 102.7 degrees and paramedics transported her to a local emergency room. *Id.* Medical records reveal that S.B. suffered a febrile seizure, and she was discharged the same day. *Id.* at 4.

Over the next year, S.B. experienced common childhood illnesses but continued to develop normally and receive recommended childhood vaccines. *See generally* Pet'rs' Exs. 1, 6. On October 19, 2011, Petitioners brought S.B. to her pediatrician for a rash. Pet'rs' Ex. 6 at 36. S.B.'s pediatrician diagnosed her with viral exanthem. *Id.* On November 6, 2011, Petitioners called S.B.'s pediatrician to notify her that S.B. had been experiencing "profuse and frequent watery diarrhea" for one day. Pet'rs' Ex. 6 at 38. S.B.'s pediatrician diagnosed S.B. with acute gastroenteritis and directed Petitioners to keep S.B. hydrated and take her to the emergency room if symptoms worsened. *Id.* There is indication that follow-up treatment was pursued in the record.

S.B. received the HAV and flu vaccinations at issue in this case on November 11, 2011. Pet'rs' Ex. 1 at 2–3. The records reveal no subsequent medical visits until December 22, 2011, when Petitioners called S.B.'s pediatrician to complain that S.B. had been congested with a nightly cough.[7] Pet'rs' Ex. 6 at 44. S.B.'s pediatrician prescribed a ten-day course of Augmentin.[8] *Id.* The next day, Petitioners brought S.B. to her pediatrician's office, complaining that S.B. had been having temper tantrums and was not holding her left arm as she normally did. *Id.* at 43. During the appointment, S.B.'s pediatrician observed S.B. "periodically fling [her] lower arm [and] hold it close to her body." *Id.* She referred S.B. to a neurologist. *Id.*

Petitioners brought S.B. to Dr. Greg Rosenn, a pediatric neurologist, on December 23, 2011. *Id.* at 125. Upon examination, Dr. Rosenn noted that S.B. had left hemiparesis with "a hemiparetic gait with circumduction of the left leg and decreased arm swing on the left." *Id.* Dr. Rosenn referred S.B. to the emergency room for neuroimaging. *Id.*

S.B. was admitted to Cohen's Children Medical Center on December 23, 2011. Pet'rs' Ex. 16 at 1. She underwent two CT scans—one of her head and one of her neck—both of which were normal. *Id.* at 54–57. On December 24, 2011, S.B. had a magnetic resonance imaging ("MRI") and a magnetic resonance angiogram ("MRA") of her brain, as well as an MRI of her cervical spine, all of which were unremarkable. *Id.* at 50–53.

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[6] Cefzil is "trademark for a preparation of cefprozil." *Dorland's* at 312. Cefprozil is "a semisynthetic, broad-spectrum, second-generation cephalosporin effective against a wide range of gram-negative and gram-positive organisms, used in the treatment of otitis media and infections of the respiratory and oropharyngeal tracts, skin, and soft tissues; administered orally." *Id.* at 312.

[7] The records do not reveal how long S.B. had been suffering from these symptoms. Pet'rs' Ex. 6 at 44.

[8] Augmentin is the "trademark for combination preparations of amoxicillin and clavulanate." *Dorland's* at 179.

On December 26, 2011, doctors transferred S.B. to the Pediatric Intensive Care Unit ("PICU") for respiratory status monitoring after she displayed poor suck and swallow ability, increased irritability, inconsolability, and weakness. Pet'rs' Ex. 22 at 26–27. S.B. was diagnosed with rhinovirus and enterovirus on December 28, 2011. *Id.* at 40. S.B. was discharged from Cohen's Children Medical Center on December 31, 2011. Pet'rs' Ex. 16 at 1.

Immediately after discharge, Petitioners took S.B. to Weill Cornell Medical Center's emergency room to get a second opinion regarding S.B.'s diagnosis. Pet'rs' Ex. 23 at 12. Dr. Murray Engel examined S.B. and noted that her symptoms were "suggestive [of a] post-infectious disorder[] involving [the] brain [and] possibl[y] [the] spinal cord and peripheral nerve and muscle." *Id.* at 20–21. Even though he noted in the medical records that S.B.'s symptoms were not "typical [of] Guillain[-]Barre [syndrome[9] ("GBS")], Dr. Engel nonetheless prescribed S.B. the typical treatment for GBS—a five-day course of IV gamma globulin. *Id.*

On January 2, 2012, Dr. Engel performed a video electroencephalogram ("EEG") on S.B. *Id.* at 59. The video EEG showed some "background slowing" and "some sharp waves and slowing in the right centrotemporal region," but "no clinical seizures." *Id.* Dr. Engel noted in the records that he needed "further data . . . lab testing[] and . . . imaging" to determine the etiology of the illness. *Id.* Dr. Engel sent S.B.'s cerebrospinal fluid ("CSF") to the Mayo Clinic for further testing related to anti-NMDAR encephalitis, and S.B. was diagnosed with anti-NMDAR encephalitis on January 11, 2012. Pet'rs' Ex. 17 at 135.

S.B. was transferred to Children's Hospital of Philadelphia ("CHOP") for further treatment on January 12, 2012. Pet'rs' Ex. 18-3 at 3; Pet'rs' Ex. 23 at 206. On January 17, 2012, S.B. began a course of Rituximab[10] infusions and a prednisone[11] taper. Pet'rs' Ex. 18-3 at 614. S.B. was transferred to CHOP's inpatient rehabilitation department on January 20, 2012, where she underwent comprehensive rehabilitation until February 8, 2012. *See* Pet'rs' Ex. 18-1 at 154–286.

On February 8, 2012, S.B. was transferred to Blythedale Children's Hospital where she underwent continued rehabilitation until March 9, 2012. Pet'rs' Ex. 9-1 at 3, 11. On April 5, 2012, S.B. was seen by Dr. Michael Fisher at CHOP. Pet'rs' Ex. 6 at 67–68. Dr. Fisher noted that S.B. was "continu[ing] to improve tremendously." *Id.* at 67.

On May 2, 2012, S.B. tested positive again for anti-NMDAR antibodies in both her CSF and serum. Pet'rs' Ex. 18-1 at 56. On June 4, 2012, S.B. finished her last round of immunotherapy and was noted to have "developmentally returned to the level of a regular [two-]year-old." Pet'rs' Ex. 6 at 63.

## III. Experts

[9] Guillain-Barré syndrome is defined as a "rapidly progressive ascending motor neuron paralysis of unknown etiology, frequently seen after an enteric or respiratory infection." *Dorland's* at 1832.

[10] Rituximab is "a chimeric murine/human monoclonal antibody that binds the CD 20 antigen; used as an antineoplastic treatment of CD20-positive, B-cell non-Hodgkin lymphoma; administered intravenously." *Dorland's* at 1650.

[11] Prednisone is "a synthetic glucocorticoid derived from cortisone, administered orally as an anti-inflammatory and immunosuppressant in a wide variety of disorders." *Dorland's* at 1509.

### A. Expert Backgrounds

#### a. Petitioner's Expert, Dr. Murray Engel, M.D.

Dr. Engel received his medical degree from the University of Chicago in 1972. Pet'rs' Ex. 27 at 1, ECF No. 34-2. He is board certified in pediatrics, psychiatry, and neurology with a special competence in child neurology and subspecialties in neurodevelopmental disabilities and clinical neurophysiology. *Id.* at 4–5. Dr. Engel's post-doctoral training includes one year spent as a pediatric resident at Yale-New Haven Hospital in New Haven, Connecticut, and an additional year spent as an adult neurology resident at the same hospital. *Id.* at 3. He also spent two years as a child neurology fellow at Columbia-Presbyterian Medical Center in New York, New York. *Id.*

Dr. Engel's clinical experience includes over forty years as an attending physician at multiple hospitals. *See id.* at 3–4. He is currently an attending physician at Yale-New Haven Hospital, Norwalk Hospital, Greenwich Hospital, Stamford Hospital, Blythedale Children's Hospital, and New York Presbyterian Hospital. *Id.* Dr. Engel has also held numerous academic positions teaching neurology, clinical neurology, pediatrics, and clinical pediatrics. *Id.* at 3. He is currently a professor of clinical pediatrics and neurology at Cornell University, a position he has held since 2008. *Id.* Dr. Engel was admitted to testify as an expert in the field of pediatric neurology. Tr. at 12.

Dr. Engel submitted one expert report and two supplemental reports in this case. *See* Pet'rs' Exs. 26, 28–29.

#### b. Respondent's Expert, Dr. Eric Lancaster, M.D., Ph.D.

Dr. Lancaster received his medical degree from the University of Maryland School of Medicine in 2003. Resp't's Ex. BB at 1, ECF No. 57-1. He completed an internship and neurology residency from 2003 to 2007, and then a neuromuscular fellowship in 2008, at the University of Pennsylvania. *Id.* He is board certified in neurology and has completed subspecialty boards in both neuromuscular medicine and neuromuscular electrodiagnostic testing. *Id.*

Dr. Lancaster has published twenty-two peer-reviewed articles. *Id.* He states in his first expert report that "many of these publications deal entirely or in large part with anti-NMDAR encephalitis and related disorders." *Id.* Dr. Lancaster worked as part of Dr. Dalmau's research team which made "many of the original discoveries in this field." *Id.* Dr. Lancaster also lectures "frequently" on anti-NMDAR encephalitis and other neurological disorders. *Id.* at 1–2.

Dr. Lancaster's clinical practice is "currently focused on autoimmune neurological diseases, and most adult patients with anti-NMDAR encephalitis at the University of Pennsylvania are followed in [his] clinic." *Id.* at 2. Over the past two years, he has directed "a quality improvement project to improve the diagnosis of anti-NMDAR encephalitis and related disorders at the University of Pennsylvania." *Id.* He notes that he "personally studied over 700 patient samples for NMDAR antibodies by several methods and measured the sensitivity and specificity of different testing methods." *Id.* Dr. Lancaster was admitted to testify as an expert in neurology and autoimmune neurological disorders and diseases. Tr. at 56.

Dr. Lancaster submitted one expert report in this case. *See* Resp't's Ex. BB.

**B. Expert Reports**

**a. Dr. Engel's First Report**

Dr. Engel submitted his first report on June 25, 2015. Pet'rs' Ex. 26, ECF No. 34-1. After reviewing S.B.'s pertinent medical history, Dr. Engel stated that "[m]y opinion, to a reasonable degree of medical certainty, is that [S.B.] developed a complex neurologic syndrome, anti-NMDA receptor encephalitis, as a direct consequence of having received [the HAV] and flu shot . . . on 11/11/11." *Id.* at 6.

Dr. Engel wrote that encephalitis generally is "inflammation of the nervous system that can result in multiplicity of neurologic signs, symptoms and disabilities[,]" including "seizures, motor deficits, coordination disorders, aphasia and other cognitive deficits." *Id.* He stated that anti-NMDAR encephalitis is "[t]he most common form of this autoimmune based encephalitis," with possibly four percent of all encephalitis patients having anti-NMDAR encephalitis. *Id.* (citing Pet'rs' Ex. 26, Tab F).

Dr. Engel described anti-NMDAR encephalitis as "an autoimmune disorder characterized by the aberrant production of IgG antibodies targeting the NMDA receptor." *Id.* These antibodies affect "synaptic function" in the brain and are "thought to be the pathogenesis of the clinical syndrome." *Id.* Additional signs of anti-NMDAR encephalitis can include "behavioral changes, movement disorders, seizures, hemiparesis, and autonomic changes." *Id.* at 6–7. In a majority of adult patients with anti-NMDAR encephalitis, "ovarian teratomas have been associated with a paraneoplastic" cause of the disorder. *Id.* However, Dr. Engel went on to explain that in approximately forty percent of all anti-NMDAR encephalitis patients, "there is no clinically detectable tumor" and thus "[t]he mechanisms triggering the disorder . . . are unknown." *Id.* (citing Pet'rs' Ex. 26, Tab K).

Dr. Engel noted there may be an infectious trigger for anti-NMDAR encephalitis in children, because "there have been infectious links to Mycoplasma, H influenza, mumps, HHV-6 and enterovirus that may occur weeks before" onset. *Id.* at 7 (citing Pet'rs' Ex. 26, Tab B). He also opined that anti-NMDAR encephalitis can be caused by vaccination. *Id.* Dr. Engel wrote, "[v]accination triggers an immune-mediated response, which impacts specific antibodies to synaptic components in the brain, specifically NMDA reception." *Id.* Dr. Engel then referenced a case study in which a patient developed anti-NMDAR encephalitis after receiving tetanus-diphtheria-acellular-pertussis ("TDaP") and inactivated polio virus ("IPV") vaccines and noted that the authors of the report concluded that "vaccines should be considered as a possible trigger of immune response in anti-NMDAR encephalitis." *Id.* (citing Pet'rs' Ex. 26, Tab C).

Dr. Engel then discussed how anti-NMDAR encephalitis is clinically diagnosed. He explained that symptoms commonly associated with anti-NMDAR encephalitis, such as "coma, aphasis, seizures, choreoathetosis and dystonia," are "associated with a variety of laboratory abnormalities." *Id.* Therefore, he explained, "[c]onfirmation of [anti-NMDAR encephalitis]

occurs by demonstrating NMDA receptor antibodies in the blood or spinal fluid." *Id.* Dr. Engel noted that doctors were able to diagnose S.B. with anti-NMDAR encephalitis after tests showed that "her CFS was positive for anti-NMDAR antibodies." *Id.*

Dr. Engel concluded that "based on S.B.'s clinical presentation and course, as well as her laboratory studies including MRI, EEG, CSF and anti-NMDA receptor antibodies, . . . she experienced a post-vaccination anti-NMDA receptor encephalitis." *Id.* Dr. Engel noted that he was one of S.B.'s treating physicians and explained that he thought that S.B. had anti-NMDAR encephalitis before it was confirmed by laboratory testing. *Id.* He wrote that he "treated [S.B.] presumptively with gamma globulin [and] steroids and then transferred [her] . . . to CHOP for further immunotherapy." *Id.* Dr. Engel then stated that S.B.'s "response to immunotherapy is demonstrative of an immune-mediated mechanism as a cause of her anti-NMDA[R] encephalitis." *Id.* (citing Pet'rs' Ex. 26, Tab J).

Dr. Engel noted that S.B.'s case was discussed in a peer-reviewed journal. *Id.* (citing Pet'rs' Ex. 26, Tab H). The case report by Goldberg et al.[12] stated that S.B.'s onset of anti-NMDAR encephalitis occurred "approximately 2 weeks" after receiving the H1N1 flu vaccine and HAV vaccine. Pet'rs' Ex. 26, Tab H, at 182. The report also stated that the presenting symptoms in infants and toddlers with anti-NMDAR encephalitis are "most commonly . . . behavioral abnormalities, movement disorders, and speech arrest, with seizures being less commonly reported." *Id.* at 183. Dr. Engel also referenced an article by Dalmau et al.[13] in which the authors note that three patients developed anti-NMDAR encephalitis after vaccination: two developed the disorder after receiving the H1N1 flu vaccine and the third after receiving the DPT vaccine. *Id.* (citing Pet'rs' Ex.26, Tab F).

Dr. Engel concluded his report by discussing the onset of S.B.'s anti-NMDAR encephalitis. Pet'rs' Ex. 26 at 8. He stated that S.B.'s "initial symptoms were approximately [five] weeks"[14] after receiving her vaccinations. *Id.* Dr. Engel again cited to the article by Dalmau et al.[15] to show that most patients, "usually less than 2 weeks [after initial onset], . . . develop psychiatric symptoms and many are seen initially by psychiatrists." *Id.* (citing Pet'rs' Ex. 26, Tab F). In toddlers, however, Dr. Engel noted, "the behavioral change can be difficult to detect because they often present with temper tantrums, hyperactivity, or irritability as opposed to frank psychosis." *Id.* Dr. Engel concluded that S.B.'s behavioral changes occurred weeks before she initially presented to the emergency room. *Id.* Therefore, "[t]he onset of her symptoms is well within the time frame for an immune[-]mediated response (5 to 42 days)." *Id.* (citing Pet'rs' Ex. 26, Tab I).

**b. Dr. Engel's First Supplemental Expert Report**

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[12] Ethan M. Goldberg et al., *Anti-N-methyl-Daspartate Receptor Mediated Encephalitis in Infants and Toddlers*. Case Report and Review of the Literature, PEDIATRIC NEUROLOGY (2014) 50:181–84.

[13] Josep Dalmau et al., *Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis*, LANCET NEUROL. (2011) 10:63–74.

[14] It is unclear why the Goldberg et al. article placed onset of S.B.'s disease as "approximately two weeks" post-vaccination while Dr. Engel wrote that it was "approximately [five] weeks" post-vaccination. *Compare* Pet'rs Ex. 26 at 8 *with* Pet'rs Ex. 26, Tab H, at 182.

[15] Dalmau et al., *supra* note 13.

Dr. Engel authored his first supplemental report on April 22, 2016, in response to Respondent's criticisms of his causation theory.[16] Pet'rs' Ex. 28, ECF No. 44-1. Specifically, Respondent argued that Dr. Engel's causation theory was improbable because "the NMDA receptors are in an 'immune privileged' state, and . . . the blood brain barrier ("BBB") would need to be breached in order for [Dr. Engel's causation theory] to work." *Id.* at 1. Dr. Engel explained that "[t]he [BBB] normally prevents antibodies from entering the nervous system in sufficient concentrations to cause disease." *Id.* at 2. He noted that while "the BBB has very low paracellular permeability[,]" certain "inflammatory reactions" or "trauma" can make the BBB more permeable. *Id.* Specifically, Dr. Engel cited to an article by Wong et al.[17] which showed that "inflammatory mediators such as cytokines produced at the inflammatory site are at least partly responsible for changes in vascular permeability." *Id.* The study demonstrated that "injections of [TNF-alpha] and [IL-1 beta] increase BBB permeability in rats, while [IFN-gamma], TNF-alpha, and lipopolysaccharide (LPS) can all increase the permeability of in vitro models of the BBB." *Id.*

Dr. Engel explained that "[i]t is well-accepted that proinflammatory cytokines instigate BBB dysfunction during neurological diseases." *Id.* at 3 (citing Pet'rs' Ex. 28, Tab C, ECF No. 79-2). Specifically, Dr. Engel wrote "[m]edical literature has demonstrated that cytokines injected intraperitoneally cross the BBB and end up in measurable quantities in various parts of the brain." *Id.* (citing Pet'rs' Ex. 28, Tab D, ECF No. 79-2). Dr. Engel cited an article by Threlkeld et al.[18] in which the authors studied the effects of IL-1 [beta] and IL-6 cytokines injected into mice and concluded that these cytokines "cross the mouse BBB by saturable transport." *Id.*

Dr. Engel then discussed the lack of epidemiological studies associating vaccination with anti-NMDAR encephalitis. *Id.* Dr. Engel noted that "[a]ny relationship between vaccination and anti-NMDA receptor encephalitis is incredibly rare, and epidemiologic[al] studies are not powered to detect rare events." *Id.* Dr. Engel also wrote that case reports "are certainly useful when discuss[ing] rare events[]" and "serve a unique purpose in the scientific and medical community by offering anecdotal evidence where experimental evidence is lacking." *Id.*

Dr. Engel concluded by addressing S.B.'s medical history, specifically some infectious exposures, unrelated to vaccination, that could have initiated an autoimmune response. *Id.* Dr. Engel noted that the Institute of Medicine ("IOM") "has repeatedly stated that the expected timeframe for an immune[-]mediated response is 5 to 42 days." *Id.* Dr. Engel again cited the Goldberg paper[19] and noted the "onset of symptoms . . . two weeks post vaccination (on or around November 25, 2011)." *Id.* Dr. Engel concluded that some of these exposures "occurred after S.B.'s symptoms began." *Id.* (emphasis in original). Specifically, "the 'otitis media noted on 12/22/2011' and the 'acute rhino-enteroviral infection as documented from a positive respiratory

[16] These criticisms are discussed in Dr. Panzer's expert report. *See* Resp't's Ex. A, ECF No. 39-1.
[17] Donald Wong et al., *Cytokines, nitric oxide, and cGMP modulate the permeability of an in vitro model of the human blood-brain barrier*, EXPERIMENTAL NEUROLOGY (2004) 190:446–55.
[18] Steven W. Threlkeld et al., *Ovine Proinflammatory Cytokines Cross the Murine Blood-Brain Barrier by a Common Saturable Transport Mechanism*, NEUROIMMUNOMODULATION (2010) 17:405–10.
[19] Goldberg et al., *supra* note 12.

sample obtained [on] 12/26/2011' occurred after the onset of [S.B.'s] symptoms, and would be a very unlikely cause or trigger" for S.B.'s anti-NMDAR encephalitis.[20] *Id.*

Dr. Engel also opined that the vaccinations are a more likely cause of S.B.'s anti-NMDAR encephalitis because the onset of symptoms—approximately two weeks—is "closer in time and well-within [sic] the peak of immune-mediated process." *Id.* Dr. Engel concluded that "several treating physicians, including [him]self, agreed that it was logical to conclude that her vaccinations were implicated in the pathogenesis of her diagnosis." *Id.*

**c. Dr. Engel's Second Supplemental Report**

Dr. Engel authored his second supplemental expert report on July 29, 2016, in response to questions from the undersigned. Pet'rs' Ex. 29, ECF No. 50-1. The undersigned asked Dr. Engel to "discuss the post-vaccination seizure S.B. had in 2010 and her concurrent otitis media and how [they] affect[ed] his opinion of the case." *Id.* Dr. Engel explained that S.B. had her ten-month well child visit on December 13, 2010, during which she received a flu shot. *Id.* At this visit, S.B. was also diagnosed with right otitis media and was prescribed Augmentin. *Id.* However, Dr. Engel noted that the records did not contain evidence that S.B. had a fever at that appointment. *Id.*

Three days later, on December 16, 2010, S.B. suffered a febrile seizure. *Id.* Dr. Engel wrote that he "briefly discussed this December 16, 2010 febrile seizure in [his] previous report to demonstrate that this child may have a predisposition to neurologic involvement following stimulation of her immune system by vaccination." *Id.* However, Dr. Engel concluded that "[t]his does not speak directly to the mechanism involved in the onset of her anti-NMDAR encephalitis, but is a notable event in her past medical history." *Id.*

The undersigned also requested that Dr. Engel "discuss what role [S.B.'s severe diarrhea on November 6, 2011, five days before she received the [HAV and flu vaccines] played, if any, and how it affect[ed] his opinion of the case." *Id.* Dr. Engel noted that the medical records surrounding this phone visit show that S.B. had "watery diarrhea for [one] day" and was "active, playful, drinking well and looked well." *Id.* Dr. Engel opined that "[t]here are many causes of watery stools, and in the absence of fever and vomiting, there is little evidence that it was caused by an infection." *Id.* at 4.

**d. Dr. Lancaster's Expert Report**

Dr. Lancaster submitted his expert report on May 15, 2017. Resp't's Ex. BB, ECF No. 57-1. Dr. Lancaster began his report by summarizing the key events in S.B.'s medical history. *See id.* at 2–5. This summary did not differ substantially from the summary provided in Dr. Engel's expert report.

Dr. Lancaster then provided background on anti-NMDAR encephalitis. *Id.* at 5. He described anti-NMDAR encephalitis as "a rare autoimmune brain disease in which the immune system generates autoantibodies to the N-methyl-D-aspartate . . . receptor." *Id.* He noted that the

[20] These potential infectious exposures were listed in Dr. Panzer's first report. *See* Resp't's Ex. A at 7. Dr. Engel submitted his first supplemental report as a rebuttal to Dr. Panzer's expert report.

disorder "affects more men than women," and the median age of patients developing the disorder is twenty years old. *Id.* Dr. Lancaster explained that some patients "may have a flu-like prodrome (a few days to [two] weeks) before the onset of symptoms." *Id.* However, he noted that "[i]t is not well understood what this prodrome is." *Id.*

Dr. Lancaster wrote that in adults with anti-NMDAR encephalitis, the first symptom is usually "psychosis and hallucinations, delusions, and inappropriate or aggressive behaviors." *Id.* In children, Dr. Lancaster stated that "[a]bnormal limb postures, abnormal gait, and dragging of a limb are particularly common symptoms." *Id.* at 6. Although seizures may occur, Dr. Lancaster stated that they "tend to remit with treatment." *Id.* Dr. Lancaster explained that some patients may enter a state of catatonia in which "they are awake but do not respond," whereas others may become "comatose, sometimes for prolonged periods [of time]." *Id.* If patients enter a comatose or catatonic state, "they often have autonomic instability, with wild swings in blood pressure and heart rate." *Id.*

In terms of recovery, Dr. Lancaster noted that "[w]ith appropriate immune therapy, most patients slowly recover over weeks to months." *Id.* He also explained that recovery is possible for patients that have entered a comatose or catatonic state, as they "may still gradually return to a normal (or almost normal) life[] with proper immune therapy." *Id.* However, he wrote that approximately six percent of anti-NMDAR patients die from the disorder. *Id.*

Dr. Lancaster explained that "[t]here are two known triggers of anti-NMDAR encephalitis." *Id.* The first is ovarian teratoma. *Id.* Dr. Lancaster described this as a "complex tumor" that "generally [has] neuronal tissue with NMDARs on it." *Id.* Dr. Lancaster opined that approximately fifty percent of anti-NMDAR encephalitis patients have an ovarian teratoma, and it is mostly seen in women of reproductive age. *Id.* He noted the possibility of other types of tumors associated with this disorder but stated that they are "much rarer and less consistent . . . [and] may be coincidence." *Id.*

Dr. Lancaster wrote that "the other known cause [of anti-NMDAR encephalitis] is a very severe preceding brain infection known as HSV encephalitis." *Id.* Dr. Lancaster described this infection as causing "severe inflammation of the brain" which requires "a massive immune response . . . to survive." *Id.* This immune response, he continued, causes that immune system to "encounter[] neurons that have been affected by viruses and the normal immune response is lost." *Id.* Dr. Lancaster opines that "[t]he presentation of a normal antigen in this context may be the trigger." *Id.*

Dr. Lancaster explained that the HSV encephalitis precedes the anti-NMDAR encephalitis by approximately seven to fifty-one days. *Id.* He discussed three articles to support this proposition. The first, by Pruss et al.,[21] "reported a series of patients with NMDAR antibodies evolving within several weeks of HSV encephalitis." *Id.* (citing Resp't's Ex. BB, Tab 3). The second, Armangue et al.,[22] presented five patients who developed clinical signs of anti-NMDAR

[21] Harald Prüss et al., *N-Methyl-D-Aspartate Receptor Antibodies in Herpes Simplex Encephalitis*, ANN. NEUROL. (2012) 72(6):902–11.

[22] Thaís Armangue et al., *Herpes Simplex Virus Encephalitis is a Trigger of Brain Autoimmunity*, ANN. NEUROL. (2014) 75(2):317–23.

encephalitis seven to forty-one days after HSV encephalitis. *Id.* (citing Resp't's Ex. BB, Tab 4). Dr. Lancaster noted that this study found that "a variety of other types of brain antibodies may be triggered by HSV encephalitis." *Id.* He used this finding to "argue[] against a specific molecular mimicry by the virus." *Id.* Rather, Dr. Lancaster argued that his theory—"exposure of brain antigens to the immune system and loss of self-tolerance in the context of life-threatening viral infection of the brain"—is a more likely explanation for how HSV encephalitis causes anti-NMDAR encephalitis. *Id.* The final article, another by Armangue et al.,[23] "reported [eight] additional cases of anti-NMDAR encephalitis occurring with a latency of [twelve to fifty-one] days." *Id.* (citing Resp't's' Ex. BB, Tab 5).

Dr. Lancaster then discussed Dr. Engel's expert report. Dr. Lancaster agreed that anti-NMDAR encephalitis is the correct diagnosis in this case. *Id.* at 7. However, Dr. Lancaster disagreed with Dr. Engel that anti-NMDAR encephalitis must have an identifiable cause. Dr. Lancaster wrote, "in about half of [anti-NMDAR encephalitis] cases no particular cause is identified." *Id.* Dr. Lancaster noted that "Dr. Engel's report ignores numerous preceding infections in a reasonable time-frame of the onset of anti-NMDAR encephalitis, which provide alternative causes." *Id.* Dr. Lancaster argued that, because of the prodrome resembling an infection seen in many anti-NMDAR encephalitis patients and a known infectious cause (HSV encephalitis), "it is more logical for infections to be triggers of anti-NMDAR encephalitis rather than vaccines." *Id.*

Dr. Lancaster further explained that molecular mimicry, proposed as a mechanism for autoimmune CNS disorders in the supporting medical literature attached to Dr. Engel's first expert report from vaccination is "very unlikely" in anti-NMDAR encephalitis cases for two reasons. *Id.* First, the autoantibodies which cause anti-NMDAR encephalitis "are highly specific for a particular part of the three[-]dimensional structure of the receptor, the 'dominant epitope' which is the same for most patients." *Id.* Dr. Lancaster wrote that "[t]hese antibodies can only target the receptor in its intact conformation in the membrane of cells." *Id.* Second, Dr. Lancaster explained that these antibodies "do not recognize other closely related proteins." He continued, "[r]eceptors that are denatured (lose their [three-]dimensional shape) cannot be recognized[]" by these antibodies. *Id.*

Dr. Lancaster also disagreed with Dr. Engel's use of case reports of individuals with anti-NMDAR encephalitis with a possible connection to other vaccinations such as TDaP and IPV. *Id.* Dr. Lancaster wrote that any association between anti-NMDAR encephalitis and these vaccines is "most likely coinci[dental]." *Id.*

### C. Expert Testimony

#### a. Dr. Engel's Testimony

Dr. Engel described anti-NMDAR encephalitis as "autoimmune," which he explained meant a "misdirected immune response where it targets parts of the body when it thinks it's targeting an external antigen or an internal stimulus." Tr. at 16:7–13. He listed "environment

[23] Thaís Armangue et al., *Autoimmune Post–Herpes Simplex Encephalitis of Adults and Teenagers*, NEUROLOGY (2015) 85:1736–43.

[and] genetics" as factors that influence autoimmunity. Tr. at 16:14–16. Dr. Engel referenced the Venkatesan et al.[24] article when discussing the mechanisms associated with autoimmunity. Dr. Engel stated that there are "multiple potential mechanisms . . . [such as] molecular imaging" but noted that "it's not absolutely clear which is operative." Tr. at 16:24–17:3.

Dr. Engel generally described the mechanism by which the HAV and flu vaccines can cause anti-NMDAR encephalitis as one where "the antibodies form in response to the stimulus and then the antibodies cross the blood-brain barrier to the brain." Tr. at 17:20–22. He stated that it is a "two-step process" where there "is a breach of the blood-brain barrier and then the antibodies gain access to the CNS." Tr. at 17:24–18:1. Dr. Engel testified that the "permeability [of] the blood-brain barrier [is impacted by] . . . proinflammatory cytokines." Tr. at 18:5–7. He stated, "[s]o basically, [H]ep A, influenza [vaccines] promote proinflammatory cytokines and that impacts the blood-brain barrier." Tr. at 18:9–11. When asked about the process of proinflammatory cytokines crossing the BBB, Dr. Engel stated, "[w]ell, we don't really know the mechanism and so . . . we're really not sure of the mechanism so we really can't explain it." Tr. at 43:20–22. He was also unable to state whether molecular mimicry played a role in S.B.'s case, stating, "[w]e don't know . . . the mechanism, so it would be speculation. I really don't have an opinion." Tr. at 43:23–44:3.

Dr. Engel testified that vaccines have been associated with anti-NMDAR encephalitis in medical literature. Tr. at 19:10–20. To support this proposition, Dr. Engel cited the case reports referenced in his written reports. First, he cited a report by Hoffman et al.[25] which discussed a patient who developed anti-NMDAR encephalitis one day after receiving the TDaP and IPV vaccines. Pet'rs' Ex. 26, Tab C. The authors of the report concluded that "[t]he onset of prodromal symptoms shortly after the immunization is intriguing and suggests the vaccination as a possible trigger of anti-NMDA[R] encephalitis." *Id.* Second, he cited Dalmau et al.[26] in which the authors discussed three patients who developed anti-NMDAR encephalitis after vaccination. Pet'rs' Ex. 26, Tab F, at 66. Third, he discussed Goldberg et al.,[27] which centered on S.B.'s case.

Dr. Engel analogized the connection between vaccines and other neurological disorders of the CNS, including "acute disseminated encephalomyelitis" ("ADEM") and "transverse myelitis" ("TM"). Tr. at 19:24–20:3. He cited to the Institute of Medicine's seminal text[28] in which the authors state that "ADEM and GBS can occur after the administration of . . . live or attenuated or killed vaccines." Pet'rs' Ex. 26, Tab I, at 47. The authors continue, "ADEM and GBS in humans . . . generally occur after an interval of [five] days to [six] weeks following infection (not clinical disease) or injection of [an] antigen." *Id.*

[24] Arun Venkatesan and David R. Benavides, *Autoimmune Encephalitis and Its Relation to Infection*, CURR. NEUROL. NEUROSCI. REP. (2015) 15(3):3.
[25] Caroline Hofmann et al., *Anti-NMDA Receptor Encephalitis After TdaP-IPV Booster Vaccination: Cause or Coincidence*, J. NEUROL. (2011) 258:500–01.
[26] Dalmau et al., *supra* note 13.
[27] Goldberg et al., *supra* note 12.
[28] Vaccine Safety Committee, ADVERSE EVENTS ASSOCIATED WITH CHILDHOOD VACCINES: EVIDENCE ON CAUSALITY 47 (Kathleen R. Stratton et al. eds., 1994).

Dr. Engel stated that there was a logical sequence of cause and effect between S.B.'s flu and HAV vaccines and her anti-NMDAR encephalitis because "[s]he was healthy beforehand. She received the vaccine[s] and then her onset of symptoms occurred within the time frame for vaccine-related anti-NMDA[R] encephalitis and [then] she responded to immunomodulatory therapy." Tr. at 20:8–12. Dr. Engel testified that he wrote "two months after immunization" in S.B.'s medical records because he "speculated that the immunizations may have been etiologic in the development of her [anti-NMDAR encephalitis]." Tr. at 22:7–16. He explained that "it seemed to be a post-infection or after-infection disorder of the nervous system," and "since this syndrome had a very . . . significant cost," he "felt that the risk of a five-day course of gamma globulin . . . was clinically warranted." Tr. at 22:24–23:8.

Dr. Engel described the onset of S.B.'s symptoms as occurring when she had "the behavioral change, insomnia, and then developed the motor problems on the left." Tr. at 24:1–9. He noted that tantrums and behavioral changes would not be easy to identify in a 22-month-old child. Tr. at 24:22–25. Dr. Engel testified that the acknowledged period of time during which immune-mediated reactions can occur is either five to forty-two days according to the Institute of Medicine or seven to fifty-one days according to Dr. Lancaster's report. Tr. at 25:19–22. He opined that, regardless of which measure is used, S.B. is "within the range." Tr. at 25:22–23.

Dr. Engel then examined potential alternative causes of S.B.'s anti-NMDAR encephalitis. Dr. Engel first discussed the respiratory virus panel by Polymerase Chain Reaction ("PCR") which showed that S.B. had rhinovirus and enterovirus on December 26, 2011. Tr. at 27:3–12. Dr. Engel testified that he did not think that either virus could be an alternative cause of S.B.'s anti-NMDAR encephalitis because "[i]t's such a common finding." Tr. at 27:11–12. He also testified that he did not think that the otitis media with which S.B. was diagnosed on December 22, 2011, could be an alternative cause because it "is a very common disorder." Tr. at 28:13–24. Dr. Engel also opined that S.B.'s upper respiratory infection mentioned in medical records from December 29, 2018, as having occurred two weeks prior could not be an alternative cause because he "[did not] think the time frame works." Tr. at 29:19–30:1.

Dr. Engel then discussed S.B.'s watery diarrhea on November 6, 2011, which resulted in a telephone visit with her primary care physician. Tr. at 30:9–31:19. He testified that he did not think an infection caused S.B.'s diarrhea because "she was active and playful and . . . drinking well, [which] does not support that she had a systemic illness." Tr. at 30:9–11. Dr. Engel also discussed S.B.'s viral exanthem, diagnosed on October 19, 2011. Tr. at 32: 21–24. He opined that this is unlikely to be an alternative cause because S.B. "had no fever, the rash was [only present] for 24 hours, [and] no testing was done." Tr. at 33:3–6.

On cross-examination, Dr. Engel was unable to say which of the vaccines S.B. received—the HAV or flu—caused her to develop anti-NMDAR encephalitis. Tr. at 42:23–43:1. Dr. Engel also agreed that, aside from ovarian teratoma and HSV, anti-NMDAR can be caused by "infectious causes." Tr. at 41:2–4. However, Dr. Engel testified that he believed that vaccines were more likely the cause of S.B.'s anti-NMDAR encephalitis than her preceding infections because of "the timing." Tr. at 43:2–4. Dr. Engel stated that the HAV vaccine causes anti-NMDAR encephalitis because "[t]he hepatitis . . . causes the body to make this antibody that then is able to cross the

blood-brain barrier." Tr. at 44:9–14. Dr. Engel also opined that the "mechanisms are the same" for how the flu vaccine can cause anti-NMDAR encephalitis. Tr. at 44:16–18.

Dr. Engel testified during questioning by the undersigned that the immune response triggered by vaccinations in general is what caused S.B.'s anti-NMDAR encephalitis, and not something specific about the HAV or flu vaccines. Tr. at 45:21–46:6. Dr. Engel was unable to list any other possible mechanisms besides molecular mimicry that could cause antibodies to cross the BBB but stated, "I think there are probably other causes." Tr. at 4613–23. He stated that he is "actually a believer [that] there probably is a genetic predisposition" to autoimmunity in order for a vaccination to trigger BBB permeability. Tr. at 47:3–8. He also opined that S.B. would have had the autoimmune response regardless of her history of infections. Tr. at 47:13–19. Dr. Engel stated, "[i]t would have occurred. I don't think she had a usual number of infections for a two-year-old child." Tr. at 47–19:20.

**b. Dr. Lancaster's Testimony**

Dr. Lancaster confirmed S.B.'s diagnosis of anti-NMDAR encephalitis. Tr. at 57:10–11. He described anti-NMDAR encephalitis as "a rare autoimmune brain disease where patients make a very specific antibody to one part of one subunit of the NMDA receptor." Tr. at 57:21–24.

Dr. Lancaster testified that "about half of [anti-NMDAR encephalitis cases are] caused by . . . ovarian teratoma." Tr. at 63:21:22. He described this tumor as "a benign tumor of the ovary." Tr. at 63:22–23. He stated that the tumor is "interesting because it has NMDA receptors" on it. Tr. at 64:1–3. He explained that ovarian teratoma causes anti-NMDAR encephalitis by "triggering the immune system [which] select[s] a clone, a group of immune cells, . . . to make . . . good antibodies to the NMDA receptor." Tr. at 111:7–12. He stated that those cells "proliferate and then produce the antibodies[.]" Tr. at 111:12–13. Dr. Lancaster conceded that "[w]e don't know precisely" at "what point . . . the tumor become[s] sufficient enough to produce a response in the body to create anti-NMDA receptor antibodies[.]" Tr. at 112:16–113:6. Dr. Lancaster stated that the mechanism by which ovarian teratoma causes anti-NMDAR encephalitis does not require the BBB to become more permeable or be breached. Tr. at 113:21–24. He explained that "many patients, on their MRI, show no evidence of any [BBB] breakdown." Tr. at 113:25–114:2.

In the other half of patients with anti-NMDAR encephalitis, Dr. Lancaster testified that "there is no tumor or there's almost never any tumor." Tr. at 16–17. He stated that in about "[two] percent" of anti-NMDAR encephalitis patients, the disease is caused by "HSV encephalitis" which is "a severe infection of the brain itself." Tr. at 64:16–20. Dr. Lancaster explained that if patients survive HSV encephalitis, then approximately "seven to seventy-four days later, anti-NMDA[R] encephalitis can occur." Tr. at 64:25–65:2. He testified that the mechanism by which HSV encephalitis causes anti-NMDAR encephalitis "is not precisely known." Tr. at 115:7–8. However, he stated that he would not classify the mechanism as "nonspecific." *Id.* at 116:3–6. He continued, "I would say [that a patient] has to generate a specific NMDA antibody to get anti-NMDA[R] encephalitis." Tr. at 116:6–8.

Dr. Lancaster testified that in approximately half of anti-NMDAR encephalitis patients overall, "there is a preceding infection in the weeks before the illness." Tr. at 656–10. He cited

to the Florance et al.[29] paper in which thirty-two adolescent anti-NMDAR patients were studied. This study found that "[p]rodromal symptoms such as fever, headache, upper respiratory symptoms, vomiting, or diarrhea were noted in [forty-eight percent] of patients." *Id.* (Pet'rs' Ex. 26, Tab K, at 3). Dr. Lancaster noted that there was "no evidence" that S.B. had an ovarian teratoma or HSV encephalitis. Tr. at 67:8–9. However, he testified that there was evidence that S.B. "experienced . . . the symptoms identified in the Florance paper." Tr. at 67:15–19. He stated that S.B. had "a viral exanthem on 10/19/2011," "gastroenteritis on 11/[7/]2011," "otitis media . . . diagnosed on 12/22/2011," and an "acute rhino enteroviral infection on 12/26[/2011]." Tr. at 67:21–68:1.

Dr. Lancaster disagreed that S.B.'s behavioral changes occurred before her movement disorder. Tr. at 94:4–6. He stated that the "dystonia seems to have [occurred] . . . as an early symptom[] of the illness . . . at about the same time [as] these nonspecific irritability behavioral change symptoms and probably . . . a little bit before changes [occurred] in her speech or at about the same time." Tr. at 94:14–19. He opined that the onset of S.B.'s anti-NMDAR encephalitis occurred sometime between December 7, 2011, and December 21, 2011. Tr. at 96:1–4. He explained that he "would favor the earlier part of that time frame as being most convincing because there [was] a clear history of symptoms of dystonia." Tr. at 68:17–19. He noted that the "abnormal posture of the limb" was diagnosed around December 7, 2011, which "would put the gastroenteritis as occurring . . . approximately 31 days" prior. Tr. at 68:20–69:2. Dr. Lancaster explained that the "clearest evidence we . . . have . . . that relates to the cases of post-HSV anti-NMDA[R] encephalitis, . . . [is that the disease occurs] . . . 7 to approximately 70 days after[] [the HSV encephalitis]." Tr. at 69:6–13. Therefore, Dr. Lancaster opined that the "gastroenteritis probably fits the timing the best" because it "fall[s] into a reasonable time frame." *Id.* at 68:7–9.

Dr. Lancaster discussed the paper he co-authored with Dr. Dalmau[30] which "attempted to provide a broad and pretty comprehensive description of anti-NMDA[R] encephalitis, what's known about the clinical features[,] . . . what's known about the treatments that have been used, what's known about causes, what's known about mechanisms and what our recommendations were for how patients should be evaluated and treated." Tr. at 71:6–12. The paper also included a description of two patients who developed anti-NMDAR encephalitis after vaccination against H1N1 flu. Tr. at 71:13–17; *see also* Resp't's Ex. EE at 5. Dr. Lancaster explained that he "thought we should include [the patients who developed the disease after vaccination] in case subsequently other cases . . . [showed that vaccinations] actually conveyed a risk of anti-NMDA[R] encephalitis." Tr. at 72:8–12. However, Dr. Lancaster stated, "[w]e have not been seeing associations with the vaccines [and anti-NMDAR encephalitis]." Tr. at 72:14–15. He opined that he did "not think there is any evidence it's more likely than not that the flu [or HAV] vaccine[s] would cause anti-NMDA[R] encephalitis." Tr. at 73:12–20.

Dr. Lancaster disagreed with Dr. Engel's causation theory because "the theory is lacking in that it doesn't explain the key feature of the disease, which is how were the specific antibodies to the NMDA receptor generated." Tr. at 74:5–8. He explained that "many things could disrupt

[29] Nicole R. Florance et al., *Anti-N-Methyl-D-Aspartate Receptor (NMDAR) Encephalitis in Children and Adolescents*, ANN. NEUROL. (2009) 66(1):11–18.
[30] Dalmau et al., *supra* note 13.

the blood-brain barrier," and even if vaccines could disrupt the BBB, "it doesn't explain where . . . the specific antibodies come from." Tr. at 74:16–21.

Dr. Lancaster also testified that "at some level, antibodies are naturally found in the brain." Tr. at 75:2–5. He explained that "there are pathways for a certain level of antibodies to be sort of transported across the blood-brain barrier to enter the brain just from your circulation." Tr. at 75:12–15. He stated that this is "a very normal process and . . . [it doesn't mean that] the [BBB is] disrupted because it's letting certain cells that are supposed to get through at low levels get through . . . and seals up immediately behind them without causing any damage to the brain or loss of integrity" of the BBB. Tr. at 75:12–76:10. In anti-NMDAR encephalitis patients, "the response . . . starts peripherally. It's an important part of the disease for these immune cells often to move into the brain and cause . . . intrathecal production, production of antibod[ies] inside the brain." Tr. at 76:15–22. Dr. Lancaster explained that "[t]he [BBB] is not broken down[,]" and in many patients—including S.B.—the "brain MRI is normal." Tr. at 76:23–25. He opined that "this idea that the [BBB] itself breaking down is either an important part of [anti-NMDAR encephalitis] or sufficient to cause the disease" is not correct. Tr. at 77:15–18.

Dr. Lancaster testified that the IOM "has looked at several conditions, such as ADEM and [GBS] that have been associated with certain vaccinations. They propose somewhat different time windows . . . [but] have not . . . addressed . . . anti-NMDA[R] encephalitis at all." Tr. at 102:13–19. He agreed that there is a connection between vaccination and GBS and ADEM. Tr. at 104:23–105:6. However, he noted that ADEM is "quite distinct from anti-NMDA[R] encephalitis because it involves an immune response against the myelin . . . and doesn't involve specific antibodies to the NMDA receptor." Tr. at 102:23–103:4.

Dr. Lancaster agreed that both the HAV and flu vaccines have been shown to increase the production of proinflammatory cytokines. Tr. at 122:9–13;103:15–18. However, he stated that the increase in proinflammatory cytokines—even if it caused a change in the permeability of the BBB or a breach in the BBB—"still doesn't get us close to understanding how someone would develop [the antibodies necessary to develop] anti-NMDA[R] encephalitis." Tr. at 122:20–22. He analogized it to injecting "an adjuvant, which is designed to stimulate the immune system[,] . . . directly into someone's temporal lobe, I might well be able to generate in a percentage of people an autoimmune disease targeting multiple brain proteins." Tr. at 116:13–16. However, he stated that "there still has to be that specific NMDA antibody or they don't get [anti-NMDAR encephalitis." Tr. at 116:16–18. Dr. Lancaster also stated that "[t]he only reason I'm discussing the [BBB] issue at all is [it] was proposed as a mechanism by [Dr. Engel] and I felt compelled to respon[d] . . . and say [that] I don't think [it] is a very good mechanism." Tr. at 141:22–142:1.

Dr. Lancaster agreed that "viral infections are also . . . as ubiquitous as vaccinations with children." Tr. at 132:16–20. He stated that if "we had looked at all of these children with anti-NMDA[R] encephalitis and we were seeing vaccinations as the common antecedent event several weeks before the onset of the illness and we were rarely seeing infections, that would make vaccinations the likely cause." Tr. at 131:16–21. He continued, "[i]nstead . . . [there is] this strong association with half of [the patients] having infections, [and] the vaccine causes being these occasional case reports that are likely chance[.]" Tr. at 132:1–4. He explained that if there were an association between vaccinations and anti-NMDAR encephalitis, it would have a stronger

degree of evidence because "[t]he children, at a young age, . . . have so many vaccinations that just by pure coincidence" there could be onset of anti-NMDAR encephalitis within one or two months of a child receiving a vaccination. Tr. at 132:8–13. Therefore, even though vaccinations and viral infections are equally ubiquitous in children, infections are more likely the cause because "we have the association [of preceding infections and] anti-NMDA[R] encephalitis with a much, much stronger degree of evidence" than with anti-NMDAR encephalitis and vaccinations. Tr. at 132:18–20.

## IV. The Applicable Legal Standard

To receive compensation under the Vaccine Act, Petitioners must demonstrate either that: (1) S.B. suffered a "Table injury" by receiving a covered vaccine and subsequently developing a listed injury within the time frame prescribed by the Vaccine Injury Table set forth at 42 U.S.C. § 300aa-14, as amended by 42 C.F.R. § 100.3, or (2) that she suffered an "off-Table injury," one not listed on the Table as a result of her receipt of a covered vaccine. *See* 42 U.S.C. §§ 300aa-11(c)(1)(C); *Moberly v. Sec'y of Health & Human Servs.*, 592 F.3d 1315, 1321 (Fed. Cir. 2010); *Capizzano v. Sec'y of Health & Human Servs.*, 440 F.3d 1317, 1319–20 (Fed. Cir. 2006). Petitioners do not allege a Table injury in this case; thus, they must prove that S.B.'s injury was caused-in-fact by a Table vaccine.

To establish causation-in-fact, Petitioners must demonstrate by a preponderance of the evidence that the vaccine was the cause of the injury. 42 U.S.C. § 300aa-13(a)(1)(A). Petitioners are required to prove that the vaccine was "not only a but-for cause of the injury but also a substantial factor in bringing about the injury." *Moberly*, 592 F.3d at 1321–22 (*quoting Shyface v. Sec'y of Health & Human Servs.*, 165 F.3d 1344, 1352–53 (Fed. Cir. 1999)).

In the seminal case of *Althen v. Sec'y of Health and Human Servs.*, the Federal Circuit set forth a three-pronged test used to determine whether a petitioner has established a causal link between a vaccine and the claimed injury. *See* 418 F.3d 1274, 1278–79 (Fed. Cir. 2005). The *Althen* test requires the petitioner to set forth: "(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." *Id.* at 1278. To establish entitlement to compensation under the Program, Petitioners are required to establish each of the three prongs of *Althen* by a preponderance of the evidence. *See id.*

Specifically, under the first prong of *Althen*, a petitioner must offer a scientific or medical theory that answers in the affirmative the question "can the vaccine(s) at issue cause the type of injury alleged?" *See Pafford v. Sec'y of Health & Human Servs.*, No. 01-0165V, 2004 WL 1717359, at *4 (Fed. Cl. Spec. Mstr. July 16, 2004), *aff'd*, 64 Fed. Cl. 19 (2005), *aff'd*, 451 F.3d 1352 (Fed. Cir. 2006). To satisfy this prong, a petitioner's theory must be based on a "sound and reliable medical or scientific explanation." *Knudsen v. Sec'y of Health & Human Servs.*, 35 F.3d 543, 548 (Fed. Cir. 1994). Such a theory must only be "legally probable, not medically or scientifically certain." *Id.* at 548–49. This may be accomplished in a number of ways.

"Reliability and plausibility of [ ] pathogenesis can be bolstered by providing evidence that at least a sufficient minority in the medical community has accepted the theory as to render it credible." *Pafford*, 2004 WL 1717359, at *4. Additionally, "epidemiological studies and an expert's experience, while not dispositive, lend significant credence to the claim of plausibility." *Id.* "Articles published in respected medical journals, which have been subjected to peer review, are also persuasive."[31] *Id.*

In addition to showing that the vaccine at issue can cause a particular injury, a petitioner must also, under *Althen's* second prong, prove that the vaccine actually did cause the alleged injury in a particular case. *See Pafford*, 2004 WL 1717359, at *4; *Althen*, 418 F.3d at 1279. The second *Althen* prong requires proof of a logical sequence of cause and effect, usually supported by facts derived from a petitioner's medical records. *Althen*, 418 F.3d at 1278; *Andreu v. Sec'y of Health & Human Servs. of Health & Human Servs.*, 569 F.3d 1367, 1380 (Fed. Cir. 2009); *Capizzano*, 440 F.3d at 1326; *Grant v. Sec'y of Health & Health Servs.,* 956 F.2d 1144, 1148 (Fed. Cir. 1992). Medical records are generally viewed as particularly trustworthy evidence, because they are created contemporaneously with the treatment of the patient. *Cucuras v. Sec'y of Health & Human Servs.*, 993 F.2d 1525, 1528 (Fed. Cir. 1993). A petitioner does not meet this obligation by showing only a temporal association between the vaccination and the injury; instead, the petitioner "must explain *how* and *why* the injury occurred." *Pafford*, 2004 WL 1717359, at *4 (emphasis in original).

Although a temporal association alone is insufficient to establish causation, under the third prong of *Althen*, a petitioner must show that the timing of the injury fits with the causal theory. *See Althen*, 418 F.3d at 1278. For example, if the petitioner's theory involves a process that takes several days to develop after vaccination, an injury that occurred within a day of vaccination would not be temporally consistent with that theory. Conversely, if the theory is one that anticipates a rapid development of a reaction post-vaccination, the development of the alleged injury weeks or months post-vaccination would not be consistent with that theory. Causation-in-fact cannot be inferred from temporal proximity alone. *See Grant*, 956 F.2d at 1148; *Thibaudeau v. Sec'y of Health & Human Servs.*, 24 Cl. Ct. 400, 403–04 (1991); *see also Hasler v. United States*, 718 F.2d 202, 205 (6th Cir. 1983) ("Without more, [a] proximate temporal relationship will not support a finding of causation.").

A petitioner who demonstrates by a preponderance of the evidence that she suffered an injury caused by vaccination is entitled to compensation, unless Respondent can demonstrate by a preponderance of the evidence that the injury was caused by factors unrelated to the vaccination. *See Althen*, 418 F.3d at 1278; *Knudsen*, 35 F.3d at 547.

[31] Both parties filed medical and scientific literature in this case, but not every filed item factors into the outcome of this decision. While the undersigned has reviewed all of the information filed in this case, only those articles and records that are most relevant to the decision will be discussed. *Moriarty v. Sec'y of Health & Human Servs.*, 844 F.3d 1322, 1328 (Fed. Cir. 2016) ("We generally presume that a special master considered the relevant record evidence even though he does not explicitly reference such evidence in his decision.") (citation omitted); *see also Paterek v. Sec'y of Health & Human Servs.*, 527 F. App'x 875, 884 (Fed. Cir. 2013) ("Finding certain information not relevant does not lead to—and likely undermines—the conclusion that it was not considered.").

## V. Discussion

### A. Experts

In this case, the experts presented by Petitioners and Respondent agree on S.B.'s diagnosis of anti-NMDAR encephalitis. Both Dr. Engel and Dr. Lancaster are board certified in neurology, and Dr. Engel has a special competence in child neurology. Dr. Lancaster's clinical practice focuses on autoimmune neurological diseases, and his clinic regularly sees all of the adult anti-NMDAR encephalitis patients at the University of Pennsylvania hospital. Dr. Lancaster has also personally studied numerous samples of NMDAR antibodies. In addition, Dr. Lancaster has published twenty-two peer-reviewed articles, most of which focus on anti-NMDAR encephalitis. In fact, Dr. Lancaster is a co-author of one of the articles cited by both parties. *See* Pet'rs' Ex. 26, Tab F; *see also* Resp't's Ex. DD. Dr. Engel has treated only one or two patients with anti-NMDAR encephalitis, one of whom is S.B.

Dr. Engel also seemed less familiar with S.B.'s medical record during parts of his testimony. For example, Respondent's counsel asked Dr. Engel whether he "agree[d] that S.B. was diagnosed with an upper respiratory infection on August 2nd, 2001[.]" Tr. at 37. Dr. Engel directed his response to Petitioners' counsel, asking, "[t]oo many dates here. Is that accurate?" Tr. at 37. In addition, Petitioners' counsel asked Dr. Engel if he "was able to locate any contemporaneous medical records diagnosing S.B. with a[n upper respiratory infection ("URI");]" to which Dr. Engel replied, "I don't recall, but if you could direct me to it, I might have." *Id.* at 30. These examples suggest that Dr. Engel did not conduct as thorough a review of the medical records prior to the hearing, when compared to Dr. Lancaster. For these reasons, Dr. Lancaster's testimony explaining S.B.'s medical history was more persuasive.

The undersigned is aware that Dr. Engel is not only a testifying expert on behalf of Petitioners but also one of S.B.'s treating physicians. Under the Vaccine Program, a treating physician's notes are usually considered more persuasive than an expert relying solely on the written record. *Capizzano*, 440 F.3d at 1326 (noting that "treating physicians are likely to be in the best position to determine whether a logical sequence of cause and effect show[s] that the vaccination was the reason for the injury." (quoting *Althen*, 418 F.3d at 1280) (internal quotation marks omitted)); *but see Snyder v. Sec'y of Health & Human Servs.*, 88 Fed. Cl. 706, 745 n.67 (2009) (noting "there is nothing in *Andreu* that mandates that the testimony of a treating physician is sacrosanct—that it must be accepted in its entirety and cannot be rebutted."). However, the undersigned will not afford substantial deference to Dr. Engel because of his relative inexperience treating anti-NMDAR encephalitis. Dr. Engel conceded during his testimony that he had seen only two or three patients during his career with anti-NMDAR encephalitis, including S.B. He has not published any articles on this disease, nor has he done any research on it. When compared with Dr. Lancaster, the difference in experience with anti-NMDAR encephalitis is significant. Dr. Lancaster has treated or diagnosed approximately forty patients with anti-NMDAR encephalitis throughout his career. He has published twelve peer-reviewed articles discussing and analyzing anti-NMDAR encephalitis. Dr. Lancaster also directed a "project to improve the diagnosis of anti-NMDAR encephalitis," where he "personally studied over 700 patient samples for NMDAR antibodies [using] several methods and measured the sensitivity and specificity of different testing methods." Resp't's Ex. BB at 2. In light of these differences in experience level with anti-

NMDAR encephalitis, Dr. Engel's opinion as it relates to the cause of S.B.'s injuries will not be given the level of deference normally afforded to treating physicians with a relevant specialty.

### B. *Althen* Prong One

Petitioners have failed to present by a preponderance of the evidence a medical theory causally connecting the HAV and flu vaccines to S.B.'s anti-NMDAR encephalitis. It is unclear exactly what theory Petitioner is advancing and the undersigned was forced to parse one together from Dr. Engel's reports and testimony. It seems that Dr. Engel is proposing that an increase in proinflammatory cytokines caused by the vaccinations resulted in a breakdown of the S.B.'s BBB. NMDA receptor antibodies, also created as a result of the vaccine-induced immune response, were then able to enter S.B.'s brain and attach to the NMDA receptors, thus leading to anti-NMDAR encephalitis.

Petitioners fail on prong one because they have not articulated a theory by which the HAV and flu vaccines create the specific antibody necessary for anti-NMDAR encephalitis to occur. In their pre-hearing brief, Petitioners cite the Venkatesan and Benavides[32] article to explain mechanisms by which "infection can lead to [the] breaking of the CNS immune tolerance[.]" Pet'rs' Pre-Hr'g Br. at 33, ECF No. 70 (quoting Pet'rs' Ex. 26, Tab B, at 2). Petitioners then list the following mechanisms: "molecular mimicry, change in antigen expression, alternative splicing, posttranslational modification, covalent modification, enzymatic processing, protein misfolding, unmasking of cryptic neural epitopes, dysregulation of immune regulators, bystander activation, and 'epitope spreading' in the infectious microenvironment." *Id.* (quoting Pet'rs' Ex. 26, Tab B, at 2). Ultimately, Dr. Engel testified that he did not have an opinion on whether molecular mimicry has any role in his causation theory because "it would be speculation." Tr. at 38.

The Vaccine Act, pursuant to the preponderance standard, does not require identification and proof of specific biological mechanisms. *Althen*, 418 F.3d at 1280 (quoting *Knudsen*, 35 F.3d at 549). In fact, the very nature of the program anticipates that vaccine injury is a "field bereft of complete and direct proof of how vaccines affect the human body." *Id.* Although Petitioners are correct that they do not need to provide the specific components of the mechanism by which the vaccines at issue can cause anti-NMDAR encephalitis, they do need to propose something more than taking a vague "kitchen sink" approach and listing eleven mechanisms that have been previously submitted in the Program for claims of vaccine-caused injury with various degrees of success. Petitioners have listed many possibilities but have not identified a sound and reliable explanation that can be applied to the vaccines and injury in this case.

Both experts agreed that anti-NMDAR encephalitis requires a very specific antibody to manifest. Dr. Engel was unable, both in his reports and his testimony, to link either the HAV or the flu vaccine—or a combination of both—to this antibody. As Dr. Lancaster explained, "[a]nti-NMDAR encephalitis involves an extremely specific antibody response against a specific three-dimensional epitope on the NMDAR. . . . These antibodies are the core element of the disease[.]" Resp't's Ex. BB at 7. Dr. Lancaster further explained that "[d]enatured viral proteins in a vaccine have no structural relationship to the NMDAR, and it would be very unlikely for these proteins to

[32] Venkatesan & Benavides, *supra* note 18.

induce the specific antibody response to the NMDAR that is necessary for anti-NMDAR encephalitis." *Id.* By comparison, Dr. Lancaster testified that ovarian teratomas "ha[ve] the fully intact NMDA receptor on it. So . . . that makes a very good stimulus for developing the antibody." Tr. at 85. He also hypothesized that in HSV encephalitis patients, the "natural receptors in the temporal lobe [are] . . . expressed in the setting of an overwhelming viral infection that stimulates the immune system incredibly strongly. . . . And in that setting, there can be a loss of self-tolerance. [A patient] can be exposed to an NMDA receptor and perhaps generate these pathogenic antibodies to it." *Id.* at 85. Dr. Engel provided no persuasive evidence that the HAV and flu vaccines can stimulate the production of the necessary antibodies.

The only medical literature provided by Dr. Engel to support the proposition that vaccines can cause anti-NMDAR encephalitis is in the form of case reports. One such report, by Hofmann et al.,[33] discusses a patient who developed anti-NMDAR encephalitis one day after receiving the TDaP and IPV vaccines. Petitioners are correct that the authors of the report conclude that "[t]he onset of prodromal symptoms shortly after the immunization . . . suggests the vaccination as a possible trigger of [anti-NMDAR encephalitis]." Pet'rs' Ex. 26, Tab C, at 1. However, this case report lacks in-depth analysis of the patient's specific medical history and the authors do not go further than a suggestion of possible causality. It does not provide sufficient support for a conclusion that the vaccines did in fact cause this patient to develop anti-NMDAR encephalitis.

Another case report that Dr. Engel discussed in his report and his testimony is the article by Dalmau et al. Dr. Lancaster is a named co-author of this study. Dr. Engel noted in his testimony that "Dr. Lancaster was involved with Dr. Dalmau in describing two patients who developed [anti-NMDAR encephalitis] after vaccination against H1N1." Tr. at 19. However, as Dr. Lancaster explained during his testimony, he included these patients in this study "in case subsequently other cases . . . [showed that vaccinations] actually conveyed a risk of anti-NMDA[R] encephalitis." Tr. at 72. This report is not persuasive evidence for Petitioners for two reasons. First, the authors do not state a belief that vaccines can cause anti-NMDAR encephalitis. In fact, Dr. Lancaster testified that "[w]e have not been seeing associations with the vaccines." Tr. at 72. As he is a credited co-author of this report, Dr. Lancaster's statements regarding this article are most pertinent. His statements that he and Dr. Dalmau included these cases only "in case subsequently other cases . . . [showed that vaccinations] actually conveyed a risk of anti-NMDA[R] encephalitis," weaken any purported link between the vaccines and the disease. Second, the article notes that the information regarding the vaccination of these patients was obtained by "personal observation."

Finally, Dr. Engel argued that S.B.'s case report was particularly probative evidence.[34] The authors of the paper wrote that S.B. "was a previously healthy, developmentally normal 21-month-old girl." Pet'rs' Ex. 26, Tab H, at 2. As Dr. Lancaster discussed in his report, this statement demonstrates that "the authors were either unaware of the infectious illnesses preceding the onset of anti-NMDAR encephalitis or chose not to include this information in their case report." Resp't's Ex. BB at 11. The authors' decision, whether knowing or not, to omit this key information renders this case report less persuasive.

[33] Hofmann et al., *supra* note 24.
[34] Goldberg et al., *supra* note 12.

While the Vaccine Act allows for circumstantial evidence to demonstrate causality, *see Althen*, 418 F.3d 1280, case reports documenting only four cases of anti-NMDAR encephalitis following vaccination is not enough to meet Petitioners' burden. These case reports, while submitted to indicate a possible association between vaccinations generally and anti-NMDAR encephalitis are not, in and of themselves, enough to demonstrate causality. Dr. Lancaster's own stated belief that these cases are more than likely "coincidence" is more persuasive than Dr. Engel's interpretation of Dr. Lancaster's research. Resp't's Ex. BB at 7.

During his testimony and in his reports, Dr. Engel discussed pro-inflammatory cytokines and the breakdown of the BBB at length. He testified that while the BBB "normally prevents antibodies from entering the nervous system in sufficient concentrations to cause disease[,]" certain "inflammatory reactions" or "trauma" can make the BBB more permeable and allow in antibodies that can cause disease. Pet'rs' Ex. 28 at 2. However, he could not describe the mechanism by which the inflammatory cytokines break down the BBB. Rather, he stated that "[w]ell, we don't really know the mechanism and so . . . we're really not sure of the mechanism so we really can't explain it." Tr. at 43.

Dr. Lancaster's testimony on this subject, on the other hand, was highly persuasive. He noted that Dr. Engel "d[id] not provide any citations that the relevant vaccines can actually cause production of these cytokines in sufficient levels to actually change [BBB] permeability." Resp't's Ex. BB at 8. More importantly, Dr. Lancaster stated that the BBB issue was a red herring because, even if pro-inflammatory cytokines break down the BBB as Dr. Engel proposed, "there still has to be that specific NMDA antibody or [you] don't get [anti-NMDAR encephalitis]." Tr. at 116. Dr. Lancaster also testified that in many anti-NMDAR patients, "[t]he [BBB] is not broken down" and the "brain MRI is normal." *Id.* at 76. In fact, Dr. Lancaster stated that he only discussed the BBB in his report and during his testimony because it "was proposed as a mechanism by [Dr. Engel] and [he] felt compelled to respon[d] . . . and say [that he doesn't] think [it] is a very good mechanism." *Id.* at 141–42.

Petitioners have not presented "a medical theory causally connecting the [HAV and flu] vaccinations and [anti-NMDAR encephalitis]." *Althen*, 418 F.3d at 1278. Therefore, Petitioners have not met their burden under *Althen* prong one.

### C. *Althen* Prong Two

Neither party disputes that S.B. developed anti-NMDAR encephalitis after she received the HAV and flu vaccinations. However, that chronology of events alone is not sufficient under the preponderant standard. Both experts agreed that there are two definitive causes of anti-NMDAR encephalitis: ovarian teratoma and HSV encephalitis, neither of which was present in S.B.'s case. Both experts also agree that prior infections have been linked in medical literature to anti-NMDAR encephalitis in some fashion. They disagree, however, on whether vaccines can cause this disease.

Dr. Engel provided no evidence that the vaccines at issue created the type of antibody required for anti-NMDAR encephalitis. Dr. Engel did not explain what, aside from "timing" of the onset, led him to conclude that the vaccinations caused S.B. to develop anti-NMDAR encephalitis. Dr. Lancaster, on the other hand, testified that "none of the cytokines or cell signaling

molecules directly interact with the receptor. None of them are really a sufficient cause for someone to develop [anti-NMDAR encephalitis]." Tr. at 82. He also explained that the vaccines "are denatured viral proteins that have no structural relationship to the NMDA receptor at all and they're . . . broken apart, they don't have that three-dimensional structure." *Id.* at 84. Therefore, the viral proteins in the vaccine are incapable of attaching to the receptor and cannot cause this disease.

Dr. Engel's theory requires a breakdown of the BBB by pro-inflammatory cytokines. However, Dr. Engel was unable to provide any evidence that S.B.'s BBB actually broke down, and S.B.'s levels of pro-inflammatory cytokines were never measured. Furthermore, Dr. Lancaster testified that S.B. did not exhibit the "sort of infectious or parainfectious symptoms" that result from an increase in pro-inflammatory cytokines and a BBB breakdown. Tr. at 81. In fact, S.B.'s brain MRI was normal. Without any evidence of a breakdown in S.B.'s BBB, Dr. Engel's theory cannot be applied to S.B.'s case.

In sum, Dr. Engel failed to demonstrate "a logical sequence of cause and effect showing that the vaccination was the reason for the inquiry." *Althen*, 418 F.3d at 1278. He did not provide evidence that the vaccines S.B. received can create the type of antibody necessary to cause anti-NMDAR encephalitis, nor that S.B.'s BBB was compromised or had increased permeability. For those reasons, Petitioners have failed at prong two.

### D. *Althen* Prong Three

Dr. Engel's proposed timeframe for disease onset was five to forty-two days post-vaccination. Pet'rs' Ex. 26 at 7. He proposed this time frame because it is the timeframe listed by the IOM for post-vaccination development of ADEM and GBS.[35] Dr. Lancaster proposed a nine to seventy-four day latency period. Resp't's Ex. BB at 8. He explained that he chose this time frame because it is the time frame for confirmed post-HSV encephalitis triggered anti-NMDAR encephalitis. Tr. at 69.

The undersigned does not need to make a determination regarding which proposed time frame is correct. S.B. received the HAV and flu vaccines on November 11, 2011. Both experts agree that onset occurred sometime before December 23, 2011, the date when S.B. presented to Dr. Rosenn.[36] This onset period falls squarely within the ranges provided by both Dr. Engel and Dr. Lancaster. Although Petitioners have failed to meet *Althen* prongs one and two, Petitioners have presented preponderant evidence that S.B. developed anti-NMDAR encephalitis within an appropriate time frame. Therefore, the undersigned finds that Petitioners have met their burden under *Althen* prong three.

## VI. Conclusion

[35] Vaccine Safety Committee, *supra* note 28.

[36] Dr. Engel stated "[S.B.'s] initial symptoms were approximately five weeks after her vaccinations." Pet'rs Ex. 26 at 7. Dr. Lancaster places S.B.'s onset "most likely between [December 7, 2011] and [December 21, 2011]." Resp't's Ex. BB at 8.

Anti-NMDAR encephalitis is a rare and vicious disease that most people are not even aware of. Compounding the frustration of dealing with such a condition is the lack of information that medical professionals have to explain what is happening. Despite those difficulties, it is heartening to hear that S.B. is now doing well.

Irrespective of the diagnostic outcome for any individual petitioner, a decision on entitlement to compensation in the Vaccine Program cannot be made based on the nature and severity of the disease alone. It must reflect a thorough analysis of the evidence and a thoughtful balance against the applicable legal standards based upon probative weight and persuasiveness. Petitioners have not established that S.B.'s HAV and flu vaccines caused her to develop anti-NMDAR encephalitis. Therefore, the undersigned must **DENY** entitlement in this case.

In the absence of a timely filed motion for review filed pursuant to Vaccine Rule 23, **the Clerk of the Court is directed to ENTER JUDGMENT** consistent with this decision.[37]

**IT IS SO ORDERED.**

s/Herbrina D. Sanders
Herbrina D. Sanders
Special Master

[37] Pursuant to Vaccine Rule 11(a), entry of judgment is expedited by the parties' joint filing of a notice renouncing the right to seek review.